Context-specific genetic interaction perturbations

Metastasis is the main cause of death in cancer patients. However, most current cancer consortia have focused on primary cancer states. To gain a better understanding of the context-specific cancer fitness landscape across cancer statements, we systematically measured the association between somatic mutations and copy-number changes within the same genes across cancer types and compared their strengths of interaction between cancer statements. We found that several cancer types and cancer genes present significantly different preferences of interaction between mutations and copy-number changes and also proved that these differences are not due to medical treatments or genomic differences (manuscript in preparation). We expect that our findings will provide new insights to understand statement-specific perturbations and clues to develop better treatments for cancer patients.

Defining new cancer predisposition genes

Although large-scale cancer genomics data are rapidly accumulating, our understanding of cancer genes is highly biased towards somatic alterations and not germline variants. Germline frequencies are usually low, and there are several technical difficulties associated with their analysis. Since only 130 cancer predisposition genes (CPGs) are currently available, their contributions to cancer risk are underestimated. We hypothesised that germline variants in Mendelian-associated genes (OMIM genes) could contribute to increasing cancer risk. First, we proved that OMIM genes tend to have more pathogenic germline variants in cancer compared to controls (manuscript under revision). We then focused on a PAH that is associated with phenylketonuria, which presents the strongest enrichment in cancer compared to controls, and this enrichment is reproduced in other cancer data sets. Furthermore, through collaborations in South Korea, we addressed how metabolic dysfunction increases cancer risk experimentally, and we identified the possible contribution of OMIM genes as new CPGs. Currently, we are expanding this concept to predict novel CPGs, not only OMIM genes, by integrating multiple features using a machine learning approach.